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Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

99306463.3

PRIORITY DOCUMENT

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Der Präsident des Europäischen Patentamts;
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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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THE TECHNOLOGY PARTNERSHIP PUBLIC LIMITED COMPANY
Melbourn, Royston, Hertfordshire SG8 6EE
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See for original title f the application page 1 of the description

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SAMPLING/DISPENSING DEVICE

This invention relates to a positive displacement type substance sampler/dispenser.

5 One example of such a dispenser is a plunger-type pipette. Such a pipette is in common usage. It generally comprises an outer cylindrical housing having a central bore in which a plunger sits. The plunger can be slid within the bore to either dispense a substance, such as a 10 fluid or particulate matter, from an orifice in one end of the housing or, if slid in the opposite direction, to draw a fluid or particulate matter into the housing. Such a dispenser has particular benefits in that it can draw up and dispense substances with a high degree of accuracy. 15 Devices in current use do, however, have problems associated with them.

Firstly, it is extremely difficult to produce a device which has a parallel housing bore, meaning that the 20 relationship between the volume of the substance drawn up or dispensed is not linearly relative to the amount of displacement of the plunger. This is particularly true for low volume devices. Furthermore, it is extremely difficult to produce a bore to a level of accuracy which ensures that there is a tight fit between the plunger and the bore wall, 25 meaning that fluid can pass around the edges of the plunger, leading to a reduction in sampling/dispensing accuracy, and leading to a risk of leakage.

The piston is typically slightly oversize for the bore such that it forms an interference fit for sealing. To 30 accommodate this, and to allow for the draft angle on the bore, either the piston or the bore may be made from a compliant material. Examples are medical syringes having rigid polystyrene bores and rubber piston ends, or stiff polypropylene pistons with a compliant thin-walled bore. 35 An alternative sealing arrangement is to provide a lip seal at the end of the piston. These constructions have many disadvantages. In general, compliant materials cannot be

used where chemical resistance is required; it becomes increasingly difficult to injection mould bores as the diameter is reduced such that devices capable of accurate dispensing over the nanolitre range are not possible; the 5 need for a draft angle and conventional moulding techniques limits the practical length and thus the dynamic range of the pipette; and the manufacture of pistons with lip seals becomes increasingly difficult as the diameter is reduced below 1 mm.

10 Thus, present methods of construction are not suited to long bore, high accuracy, low cost and sub-microlitre devices.

15 Other problems associated with such devices includes the fact that they are difficult to handle automatically, their manufacture is costly, and it is often difficult to alter the materials from which the plunger and housing are made without changing moulding tooling for both components.

20 According to a first aspect of the present invention, there is provided a positive displacement type substance sampling and dispensing device comprising:

a central plunger formed from a first material; and
a plunger housing formed from a second material the housing being formed by moulding and setting the second material on to the surface of the plunger so that the 25 plunger can slide in the housing to draw a substance into it.

30 The first material may be metal, plastic, ceramic or other suitable material. The plunger may be formed from drawn wire or extruded material to ensure that it has a uniform diameter. The housing may be moulded onto the plunger by injection moulding, welding, coextrusion, casting, dip coating etc.

35 The materials may be selected such that, preferably, the material of the piston is stiffer and/or has a lower thermal expansion coefficient than the material of the bore. If heat is applied during manufacture, such as using molten plastic to form a bore round a metal wire, the bore

will progressively tighten around the piston as the device cools down, thus forming a better seal. If the piston can be maintained at a lower temperature than the material of the bore during forming, it is possible to get further 5 improved sealing because the piston will have expanded even less with respect to the bore. The piston may be actively cooled, or may exploit a higher thermal conductivity or specific heat capacity property than the material of the bore.

10 During its manufacture, the device may be attached or incorporated into a flexible strip to which further devices are attached for ease of automated handling.

The material of the strip may itself form part or all of the bore of the device.

15 The flexible strip may have sprocket holes to drive and align the pipettes. It may be arranged so that all of the pipettes are held in the same plane and a hinged region is provided at each pipette to allow single or multiple pipettes to be hinged away from the general plane of the 20 strip and thus be made available selectively.

The multi-pipette strip embodiment of the invention has additional benefits. A pipetting robot will typically pick a pipette tip from a rack of tips, perform an aspiration at one location and dispense liquid to another 25 before ejecting the tip to take a fresh one. The tips are located in different positions in a rack, typically 96 at a time. The robot has to be programmed for each tip position and the tips must be accurately positioned. This is difficult and problems can be experienced in tip pick 30 and drop. The number of tips that can be accessed by the robot is limited to the number which can be accommodated in the area within the robots reach. The speed of pipetting is limited by the distance that the robot has to travel, the need for positional accuracy and the need to accelerate 35 and stop a heavy robot.

According to a second aspect of the present invention, there is provided a method of substance sampling and dispensing comprising the steps of:

5 feeding a continuous strip, on which pipettes are mounted, from a supply reel to an aspirate head;

positioning one or more of the pipettes ready for sampling;

taking a sample;

10 feeding the strip to a dispensing head; and dispensing the sample.

The method of the present invention solves these problems. The pipetting robotics can be divided into many pipetting heads (aspiration and dispense) with the pipette strip running between them. The pipette strip is fed continuously from a remote reel. A fresh pipette is fed automatically to an aspirate head and is positioned to take a sample. The full pipette then leaves the aspirate head and travels to a dispense head where the sample is dispensed. The pipette may then continue on a waste reel.

20 The pipette strip is always in contact with the robotic system, eliminating alignment problems. The need to travel to a tip rack position is eliminated, as is the capacity limitations dictated by the robot's operating envelope. As the pipette strip has very low mass it can be accelerated, moved and stopped much faster than a robot leaving the aspirate and dispense heads having only to travel short distances.

30 The housing may be formed so that at one end of the device, there is provided a frangible tip which can be removed before use to prevent contamination of the device prior to use.

35 Alternatively, the device may be formed so that it has a heat sealable tip, allowing for the loading of the apparatus with a substance, the substance being sealed in place by sealing of the tip.

The device may also be incorporated into fluidic devices such as "chip-based" analytical devices, chemical

synthesizers and sensors to provide a means of forming capillaries, valves and pumps. For example,

5 The device may have plural plungers arranged on different axes and each sliding within a different region of the housing, the different regions of the housing being joined at a central common core adjacent to an aperture.

10 By forming the housing around the plunger the cost of manufacture of the device is reduced considerably. Furthermore, such a device has a highly effective seal 15 between the plunger and the housing, and can also be ensured of having a uniform cylindrical wall, even if it is arranged for the dispensing/sampling of very small samples.

15 The device may be formed by moulding the bore round a drawn wire such that it produces a pipette with a perfectly 20 cylindrical bore throughout. In use, the drawn wire may be projected beyond the tip of the device to pierce the seal of a storage vessel or to act as an ultrasonic probe or electrode for automatic level sensing. A second conductor may be provided parallel to the piston to act as a counter 25 electrode.

25 The bore may be formed round a piston which has had its tip ground to a shaped point. This provides for an aperture that is a smaller diameter than the bore at the tip of the device, which is important for retaining liquid in larger bore devices.

According to a third aspect of the present invention, there is provided a substance sampling and dispensing system comprising:

30 an aspirate head;
a supply reel for feeding to the aspirate head a continuous strip on which one or more pipettes are mounted;
positioning means for positioning the pipettes ready 35 for sampling; and
a dispensing head for receiving the strip prior to dispensing a sample.

One example of the present invention will now be described with reference to the accompanying drawings, in which:

5 Figure 1 is a schematic cross-sectional view of a known sampling/dispensing device;

Figure 2 is a side cross-sectional view of a device according to the present invention during a first stage of manufacture;

10 Figure 3 is a side cross-sectional view of a device according to the present invention after manufacture;

Figure 4 is a side view of a number of the devices according to the present invention attached to a flexible strip for ease of handling;

15 Figure 5 is a side cross-sectional view of a further example of the present invention;

Figure 6 is a perspective view of a number of the devices according to the present invention attached to a flexible strip;

20 Figure 7 is a perspective view of a number of devices according to the present invention during a sampling step;

Figure 8 shows the results of volumetric accuracy trials performed with one example of the present invention; and

25 Figure 9 shows photo-micrographs of a cross section of a pipette made by the process of example 1.

Referring to Figure 1, a prior art positive displacement-type pipette has an outer housing 1 which has a plunger 2 slidably retained therein. The plunger 2 can be moved to draw a sample into the housing 1 or expel a sample from the housing 1 via an aperture 3. The plunger 2 has a head 4 formed from relatively hard material and which is resilient enough to compensate for a variation in housing diameter with respect to the position of the plunger 2 within the housing. The disadvantages of this 30 device, in terms of difficulty of manufacture, inaccuracies and leakage problems, are discussed above.

Figure 2 is a side cross-sectional view of a device 10 in accordance with the present invention during manufacture. The device 10 has a central plunger 12, in this example formed from drawn metal, and an outer housing 11. The outer housing 11 is moulded onto the plunger 12.

If a thermoplastic (for example, but not limited to polyethylene or polypropylene) is used to form the outer housing the plunger should be formed from a material with a higher melting point and preferably lower thermal expansion coefficient than the housing. The plunger, may for example, be made of metal, glass, plastic or ceramic. The housing may also be formed from a thermoset material (for example, but not limited to silicone rubber or polyurethane resin) or a thermoplastic dissolved in solvent (for example polycarbonate or polyvinylchloride in solvent) in which case the plunger material need not have a higher melting point than the housing. It is preferable to use a thermoset that shrinks on curing.

The housing 11 may be formed by injection moulding, extrusion, or any other well known casting, ultrasonic, welding, dip-coating, co-extrusion, powder coating, thermoforming, spraying forming technique. Once the housing 11 has cooled and set the device can be trimmed to length and the plunger 12 can be drawn into the housing, leaving an aperture 13 and an inner core 14 into which a sample can be drawn during use. The inner core 14 is a uniform cylinder as it corresponds to the outer surface of the plunger 12. Furthermore, it is in extremely close engagement with the plunger 12 because of the moulding techniques employed.

Figure 4 shows how the device 10 of the present invention may be attached to one or more flexible strips 15 for ease of handling. In particular, such an arrangement is handled very easily by automated machinery. In practice, because of the extremely low cost nature of the manufacture of the device 10, it can be treated as a disposable item in use.

Variations of the construction of the device 10 are possible. Firstly, the housing 11 may be formed over the end of the plunger 12 and arranged so that, in use, it has a frangible region which can be snapped off just prior to 5 device use to prevent contamination of the plunger end. Furthermore, the device 10 may be provided with a heat sealable region adjacent to the aperture 13, so that a substance can be placed in the core 14 of the device 10 and sealed therein. This provides a sealed device that, once 10 the end is cropped off, can meter and deliver the contents without loss.

A further alternative arrangement is shown in Figure 5. In this arrangement, plural plungers 12 have a outer housing 11 formed thereon. All of the plungers 12 are able 15 to access a common core 14 and tip 13. By withdrawing the pistons, capillary paths are created in the device. Liquid can be drawn up and moved through the system very precisely by moving the pistons. Where capillaries intersect the pistons may be operated as active valves to stop or 20 regulate flow. A viewing window (not shown) may be incorporated into devices to allow the contents to be analysed by a detector. Such an arrangement provides for an extremely cost effective multiple sample withdrawal and dispensing arrangement that still has an high degree of 25 sampling/dispensing accuracy and extremely low leakage.

By withdrawing the pistons, capillary paths are created in the device. Liquid can be drawn up and moved through the system very precisely by moving the pistons. Where capillaries intersect the pistons may be operated as 30 active valves to stop or regulate flow. A viewing window (not shown) may be incorporated into devices to allow the contents to be analysed by a detector.

This type of arrangement is not limited to the simple example shown. A multitude of pumps, capillaries and 35 valves may be incorporated into three dimensional fluidic devices such as "chip-based" analytical devices, chemical synthesisers and sensors using the method of the invention.

There are now described three examples which have proved to be particularly advantageous.

Example 1

Figure 4 shows a device constructed according to the present invention. Hard drawn and polished stainless steel wire (British Standard 2056 302S26) of 0.40 mm diameter is inserted into high density polyethylene (HDPE) tubing of 0.43 mm ID and 0.66 mm OD. The tubing length is chosen as 23 mm and the wire length as 30 mm, to leave 7 mm of wire protruding. This tubing is placed across a tape 30 mm wide, made of 0.175 mm polypropylene film. The tubing with wire insert is then welded onto the backing tape using a hemi-cylindrical ultrasonic weld horn along the length of the plastic tube. This applies pressure and melts the plastic tube such that the tube material flows around the wire. This eliminates the 0.03 mm clearance between the wire and the tubing stock. A pipette is thus formed and is simultaneously welded to the backing film in one operation. Multiple pipettes can be formed in a continuous step-and-repeat process.

The tape can then be die-cut to crop the tubing and wire to form the pipette shapes and sprocket holes 16 in one operation.

The backing tape is cut to provide slender pipettes with a hinge region 17 where the piston 12 protrudes from the bore. Further pipettes have been made by the above method where the HDPE tubing and wire insert were replaced by HDPE-coated stainless steel wire formed by extrusion. These were ultrasonically welded onto the backing tape as before, or heat-welded onto a backing tape that had a layer of surlyn hot melt adhesive applied on it.

A multiple aspirate/dispense head can be constructed to grip the backing tape and pistons independently, and to drive the pistons up and down under control of a stepper drive and lead screw arrangement (not shown). In use, the tape is sprocket-fed into the dispense head lying flat (figures 6 and 7). The desired number of pipettes are then

folded through 90° at the hinge region to align the pipettes vertically. During this operation the free end of the piston moves from its protected resting position against the backing tape to a vertical position where it 5 may be accessed by the robotic actuator. In this way, the pipette array of any number can be created from a single continuous tape stock.

Volumetric accuracy trials were performed with the prototype device by aspirating 100, 200, 300, 400 and 500 10 nl samples of writing inks and dispensing them into dry receptacles with tipping off. The results were determined gravimetrically and are shown in figure 8. This shows that even non-optimised devices following this invention are capable of accurately aspirating and dispensing samples as 15 small as 100 nl.

Trials with prototype devices of the above construction were carried out to test their performance as storage devices. 100 nl of air was drawn into each device, followed by 100 nl of water and finally another 100 nl of 20 air. Devices were tested with open and sealed ends. The ends were sealed by dipping into hot wax, hot melt glue or by heat welding them close. Samples were stored for 30 days at room temperature, -20°C and -74°C. The open-ended pipettes lost weight rapidly at room temperature, losing 25 all the sample in six hours. All other samples showed no detectable weight loss over the test.

The advantage of this approach for storage is that all of the material stored can be recovered and the storage device can also be used to meter and dispense the stored 30 sample.

Figure 9 shows a photomicrograph of a cross-section of a pipette made by the process of example 1. The 0.3 mm diameter wire has been withdrawn. The out-of-round distortion was caused by the blade used to cut the section. 35 On re-inserting the wire plunger the device assumes a circular cross-section.

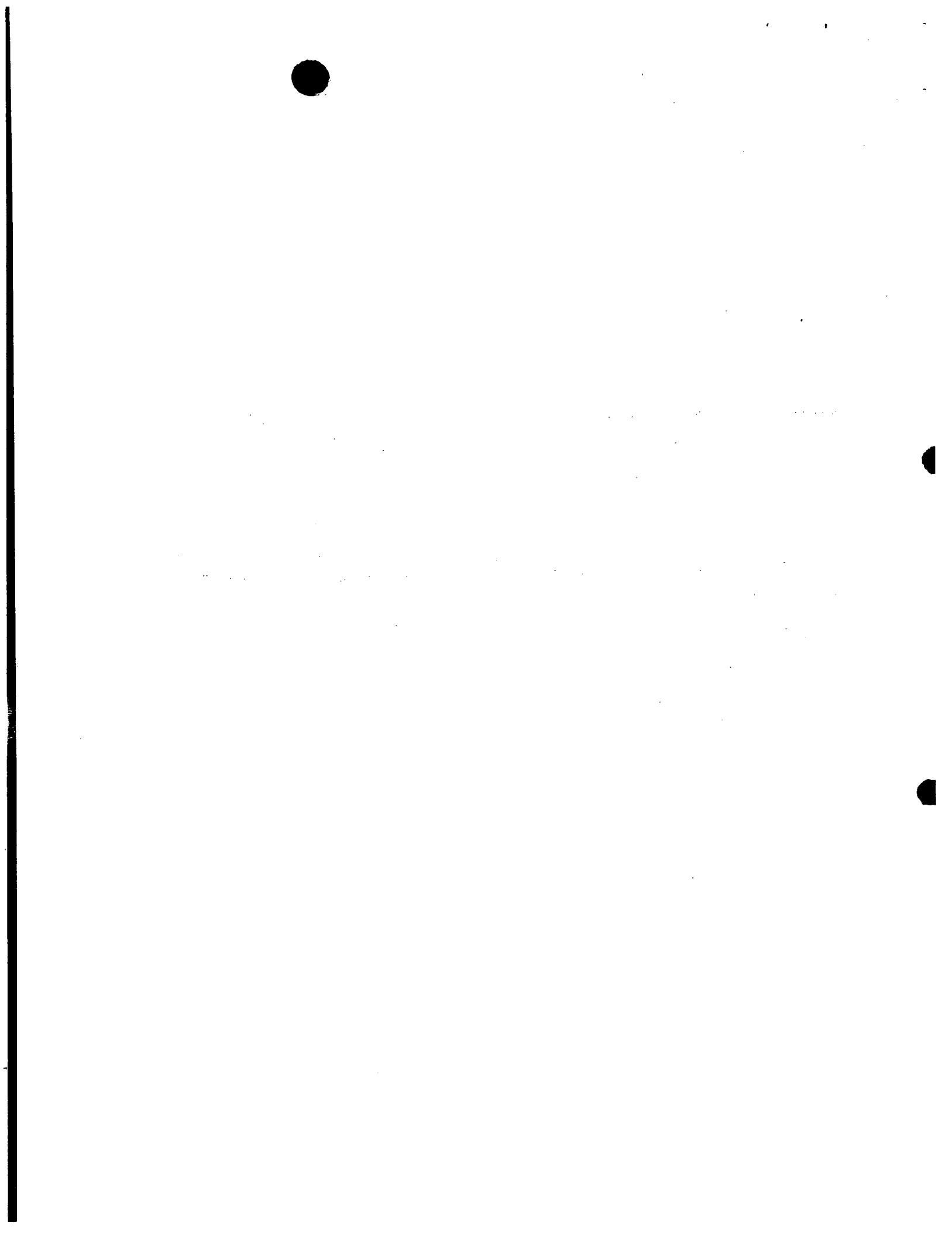
A further device was made by the method above, but using polyethylene-coated PET film for the backing tape. The PET layer provides a stiffer backing tape more suited for mechanical feed.

5 **Example 2**

A device according to present invention was constructed by insert molding 0.5 mm diameter stainless steel wire into mould-making grade silicone rubber. A mould was made from three 3 mm thick aluminium sheets 10 sandwiched between two 1 mm thick sheets of glass such that a void 100 mm long, 20 mm high and 3 mm thick was formed. The assembly was held together with spring clips and the top of this void was open to allow filling with resin. An array of stainless steel wires was suspended above the 15 mould with the ends of the wires protruding to the bottom of the mould. Silicone resin was poured into the mould and allowed to cure. Once set, the clips were released and the glass sides taken off the mould to allow the device to be removed. After shaping the pipettes with a knife the wires 20 were cropped to length to form pistons. Operation of the resulting prototype demonstrated suitable function as a pipette.

Example 3

A device according to the present invention was 25 constructed by sandwiching stainless steel entomology pins (0.38 mm diameter, 38 mm long, size 00) between polypropylene tapes 0.2 mm thick by 30 mm wide 300 mm long. The pins were laid across one plastics material and the second plastic tape was over-laid to form a sandwich. The 30 plastic sheets were joined together and heat-welded around and along the length of each individual pin between two hemi-cylindrical heated formers. This caused the polypropylene to flow around the pins, thus forming a barrel around each piston. The tape was then cut to form 35 an array of pipettes following the method of Example 1.



CLAIMS

1. A positive displacement type substance sampling and dispensing device comprising:

5 a central plunger formed from a first material; and
a plunger housing formed from a second material the
housing being formed by moulding and setting the second
material on to the surface of the plunger so that the
plunger can slide in the housing to draw a substance into
10 it.

2. A device according to claim 1, wherein the plunger is
formed from drawn wire or extruded metal.

15 3. A device according to claim 1, wherein the first
material is one of metal, plastic and ceramic.

4. A device according to any one of the preceding claims,
wherein the second material is plastics material.

20 5. A device according to any one of the preceding claims,
wherein the plunger is actively cooled during moulding.

25 6. A device according to any one of the preceding claims,
wherein the first material has a higher thermal
conductivity and/or specific heat capacity than the second
material.

30 7. A device according to any one of the preceding claims,
wherein the housing is moulded onto the plunger by one of
injection moulding, welding, coextrusion casting and dip
coating.

35 8. A device according to any preceding claim, attached
to a flexible strip, to which further devices are attached
in use.

9. A device according to any one of the preceding claims, wherein the strip has sprocket holes to drive and align the pipettes.

5 10. A device according to any one of the preceding claims, wherein the strip has a hinged region to allow single or multiple pipettes to be hinged away from the general common plane of the strip and thus be made available selectively.

10 11. A device according to any preceding claim, wherein the housing is formed so that at one end of the device there is provided a frangible tip which can be removed before use.

15 12. A device according to any of claims 1 to 11, wherein the device is formed so that it has a heat sealable tip.

13. A device according to any proceeding claim comprising plural plungers arranged on different axes and each sliding 20 within a different region of the housing, the different regions of the housing being joined at a central common core adjacent to an aperture.

14. A method of substance sampling and dispensing 25 comprises the steps of:

feeding a continuous strip, on which pipettes are mounted, from a supply reel to an aspirate head;

positioning one or more of the pipettes ready for sampling;

30 taking a sample;

feeding the strip to a dispensing head; and dispensing the sample.

15. A method according to claim 14, further comprising the 35 step of feeding the strip to a waste reel.

16. A substance sampling and dispensing system comprising:

an aspirate head;

a supply reel for feeding to the aspirate head a continuous strip on which one or more pipettes are mounted;

positioning means for positioning the pipettes ready
5 for sampling; and

a dispensing head for receiving the strip prior to dispensing a sample.

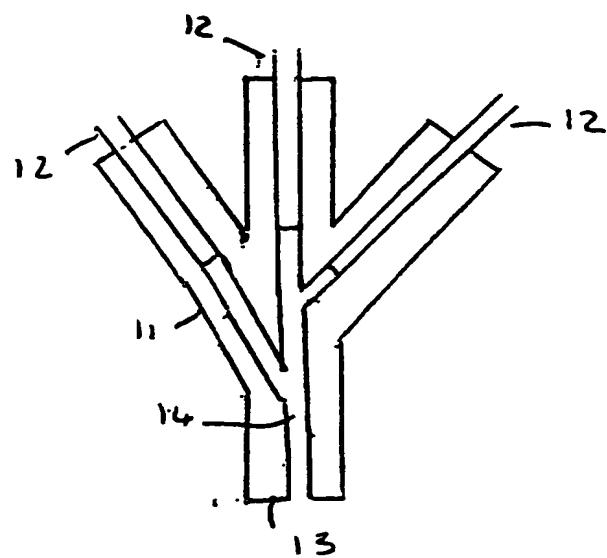
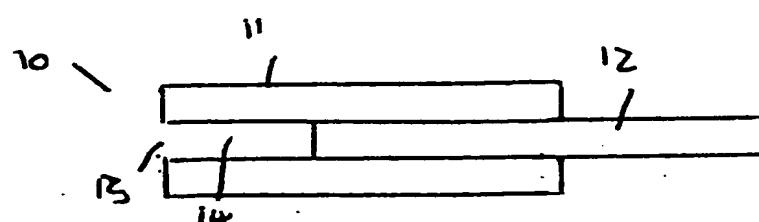
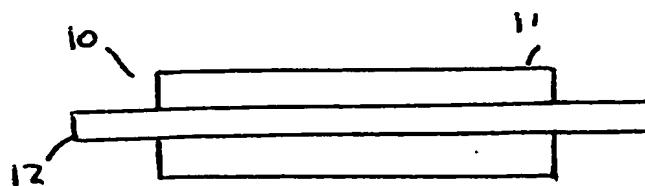
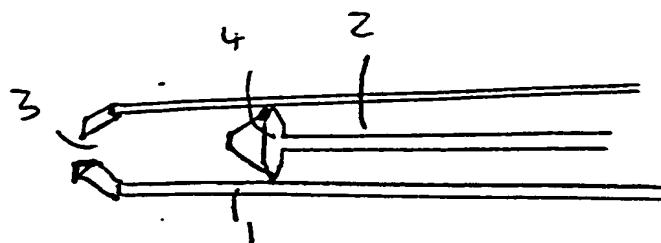
10 17. A system according to claim 16, further comprising a waste reel for receiving the pipette strip after a sample has been dispensed.

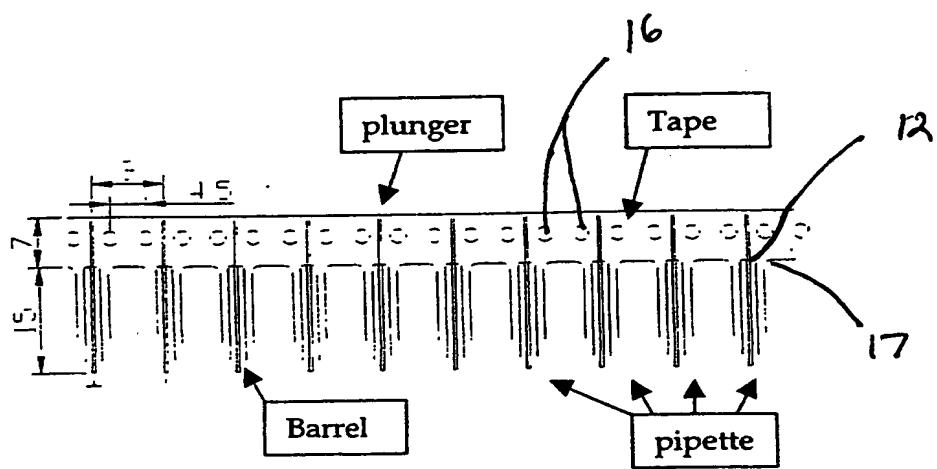
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ABSTRACT

A positive displacement type substance sampling and dispensing device comprises a central plunger formed from a first material. A plunger housing is formed from a second material having a melting point lower than the first material, the housing being formed by moulding and setting the second material on to the surface of the plunger so that the plunger can slide in the housing to draw a substance into it.

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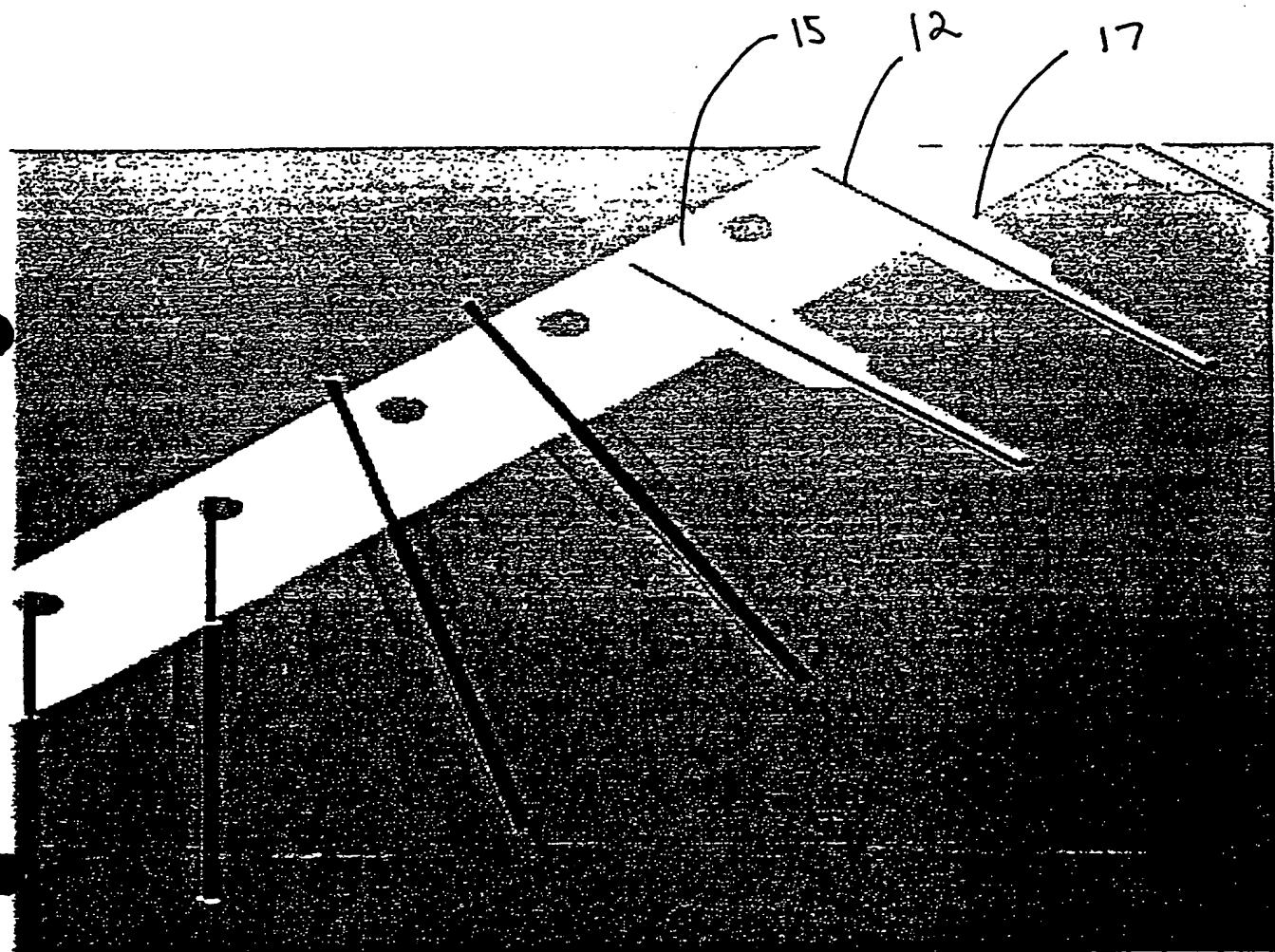
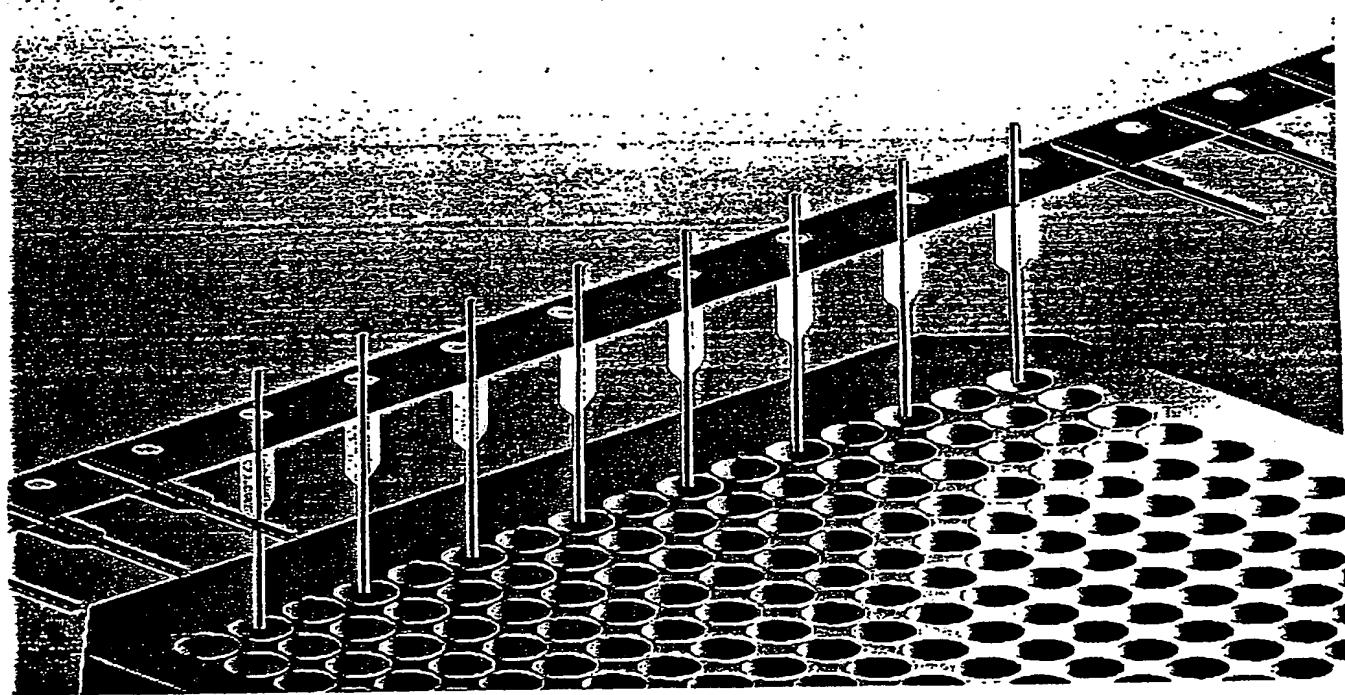


Fig. 1



Volumetric data for prototype pipettes

